Pertussis

Gary Reubenson

10 September 2014
Conflicts of Interest

• Sanofi
  – Local Conference support
  – Study sponsor

• Pfizer
  – Local & International Conference Support
  – Speakers fee

• Abbvie
  – Speakers fee
Overview

- History
- Epidemiology
- Investigation
- Management
- South African Experience
- What now?
- Questions
History

First described in Paris, 1578

Guillaume de Baillou:
‘The lung is so irritated that, in its attempt by every effort to cast forth the cause of the trouble, it can neither admit breath nor easily give it forth again. The sick person seems to swell up, and, as if about to strangle, holds his breath clinging in the midst of his jaws...’
History

• First isolated in 1906 by Bordet & Gengou
  – Fastidious, fimbriated, Gram-negative bacilli
• 1920s: first whole-cell vaccines
• 1942: combined to form DTwP
• 1974: Added to EPI
• 1981: first acellular vaccine (aP)
• 2004: complete genome sequenced (±8m bp)
Epidemiology

- Highly contagious ($R_0 = 12-17$)
- No lifelong immunity
- Droplet & Respiratory Spread
- Incubation 5-10d (up to 21d)
- Classic Pattern:
  - Catarrhal → Paroxysmal → Convalescent
- Exclusively human disease
- WHO Estimates (2008):
  - >16m cases, 95% in developing countries, 195 000 deaths (2012: 125 344) – vast majority <1y
  - 82% vaccine coverage, 687 000 deaths averted
Epidemiology

• Peaks every 3-5y
• Adults & adolescents main source of infection
• Increasing incidence in UK, France, USA, etc.
  – Waning immunity (aP vs. wP)
  – Limited subclinical boosting
  – Vaccine evasion
• Less severe in vaccinated individuals
**Figure 1: US pertussis cases reported between 1922 and 2013***

Healthcare Providers as Sources

- Transmission to patients well described
- Initiated outbreaks
- ACIP:
  - Recommends Tdap as a one-time booster
    - Unknown duration of protection
  - Post exposure prophylaxis (regardless of vaccination status)
    - generally azithromycin
Investigation

• Culture (BG/RL)
  – Insensitive
  – Most useful early

• PCR: Dacron-Rayon swab of posterior NP
  – PtxA
  – IS481:
    • 50-238 copies per genome in *B pertussis*
    • 8-10 copies per genome in *B holmesii*
    • Occasionally in *B bronchiseptica*
  – IS1001: *B parapertussis*
  – hIS1001: *B holmesii*

• Serology
  – Low sensitivity and specificity
  – Very high levels may be of value with prolonged symptoms
Management

• Largely supportive, though no evidence to support opioids or antihistamines

• Antibiotics (usually macrolide)
  – Effective if used early (catarrhal or early paroxysmal stages)
  – Generally prescribed to reduce infectivity (21 → 5d)

• Appropriate Infection Prevention & Control
Prevention

• Chemoprophylaxis
  – Family & close contacts
  – Questionable efficacy
  – Not if >21d since onset of cough
• Vaccination
  – wP, aP & ap
  – 1/2/3/4/5 components
  – Many countries adding booster doses to children, adolescents and pregnant women
• Pentaxim®:
  – Pertussis toxoid + filamentous haemagglutinin
  – NOT: Pertactin or either fimbrial agglutinogens
  – 6, 10 & 14 weeks and 18 months
• June 2011, ACIP recommended routine immunisation of pregnant women
  – All women
  – Every pregnancy
• ‘Cocooning’ – expensive & logistically challenging
Maternal Vaccination

• Why?
  – Increases transplacental Ab
  – Mothers often inadvertently transmit to infants
  – Infants vulnerable pre-vaccination

• When?
  – Pre- vs. Postpartum
  – Optimally 30-32 weeks

• Reduces Ab response when infant immunized
  – Slightly, but likely insignificant
I was a big fan of the anti-vaccine movement. Until I got really sick....
# Exposure to antigens

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Proteins</th>
<th>Vaccine</th>
<th>Proteins</th>
<th>Vaccine</th>
<th>Proteins / polysaccharides</th>
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</thead>
<tbody>
<tr>
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<td>Diphtheria</td>
<td>1</td>
<td>Diphtheria</td>
<td>1</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1</td>
<td>Tetanus</td>
<td>1</td>
<td>Tetanus</td>
<td>1</td>
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<tr>
<td>Pertussis (wP)</td>
<td>3000</td>
<td>Pertussis (wP)</td>
<td>3000</td>
<td>Pertussis (aP)</td>
<td>2–5</td>
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<tr>
<td>Polio</td>
<td>15</td>
<td>Polio</td>
<td>15</td>
<td>Polio</td>
<td>15</td>
</tr>
<tr>
<td>Smallpox</td>
<td>200</td>
<td>Measles</td>
<td>10</td>
<td>Measles</td>
<td>10</td>
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<tr>
<td></td>
<td></td>
<td>Mumps</td>
<td>9</td>
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<td></td>
<td></td>
<td>Rubella</td>
<td>5</td>
<td>Rubella</td>
<td>5</td>
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<tr>
<td></td>
<td></td>
<td>Varicella</td>
<td>69</td>
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<td><strong>Total</strong></td>
<td><strong>3217</strong></td>
<td><strong>Total</strong></td>
<td><strong>3041</strong></td>
<td><strong>Total</strong></td>
<td><strong>128–131</strong></td>
</tr>
</tbody>
</table>

Adapted from Offit *et al.* *Pediatrics* 2002;109:124–9
Effect of HIV Exposure on Vaccination

Antibody Responses to Vaccination among South African HIV-Exposed and Unexposed Uninfected Infants during the First 2 Years of Life

Brian A. Reikie, Shalena Naidoo, Candice E. Ruck, Amy L. Slogrove, Corena de Beer, Heleen la Grange, Rozanne C. M. Adams, Kevin Ho, Kinga Smolen, David P. Speert, Mark F. Cotton, Wolfgang Preiser, Monika Esser, Tobias R. Kollmann

Clinical and Vaccine Immunology January 2013 Volume 20 Number 1
The Journal of Infectious Diseases

Prevention and Control of Pertussis

S1  Can We Conquer Coqueluche?
    Ruth Lynfield and William Schaffner

S4  Pertussis Vaccine Trials in the 1990s
    Linda C. Lambert

S10 Immune Responses to Pertussis Vaccines and Disease
     Kathryn M. Edwards and Guy A. M. Berbers

S16 Mouse and Pig Models for Studies of Natural and Vaccine-Induced Immunity to *Bordetella pertussis*
     Kingston H. G. Mills and VolkerGerds

S20 Nonhuman Primate and Human Challenge Models of Pertussis
     Tod J. Monker and Scott A. Halperin

S24 Possible Options for New Pertussis Vaccines
     Bruce D. Meade, Stanley A. Plotkin, and Camille Locht

S28 Clinical Evaluation of Pertussis Vaccines: US Food and Drug Administration Regulatory Considerations
     Karen M. Farizo, Drusilla L. Burns, Theresa M. Finn, Marion F. Gruber, and R. Douglas Pratt

S32 Pertussis Resurgence: Perspectives From the Working Group Meeting on Pertussis on the Causes, Possible Paths Forward, and Gaps in Our Knowledge
     Drusilla L. Burns, Bruce D. Meade, and Nancy E. Messonnier
SA Experience

• Historical

• Bloemfontein
  • Clinician initiated, April 2008-March 2013

• Cape Town
  2. Prospective Case-control Sept 12-Sept 13

• Johannesburg
  – CHBAH (PERCH)
    • Case-control study, August 2011-13
  – RMMCH (NHLS)
    • Surveillance study from August 13

• National
  • Public & Private Sector LIS
WHOOPING COUGH IN SOUTH AFRICA *

ITS OCCURRENCE AND CONTROL

DAVID ORDMAN, B.A., M.B., CH.B., CAPE TOWN, D.P.H., RAND.

The South African Institute for Medical Research, Johannesburg.

1. Statistics of morbidity and mortality in whooping cough are considered to be unsatisfactory in that they underestimate the number of cases and deaths due to the disease.

4. It is considered that whooping cough is too lightly regarded by the public and even by medical men.

12. The question is considered of the immunization of the Native mother in the last months of pregnancy to provide passive antibodies for the new-born baby until it can be adequately protected by the use of a prophylactic vaccine.

Fig. 4. An analysis of the deaths from whooping cough, diphtheria, measles and scarlet fever in Europeans in the Union of South Africa in the nine-year period 1936-1944. (The infant deaths are shown as hatched portions of the columns.)
Bloemfontein

Pertussis Apr 2008 – Mar 2013

<table>
<thead>
<tr>
<th>Age</th>
<th>Total n=154 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4 weeks</td>
<td>15 (9.7%)</td>
</tr>
<tr>
<td>5-16 weeks</td>
<td>63 (40.9%)</td>
</tr>
<tr>
<td>17wks – 6 months</td>
<td>22 (14.3%)</td>
</tr>
<tr>
<td>7 – 12 months</td>
<td>21 (13.6%)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>33 (21.4%)</td>
</tr>
</tbody>
</table>

154 cases:
- 148 B pertussis
- 2 B parapertussis
- 2 dual infection

With Thanks to Ute Hallbauer
Bloemfontein

- 87.4% admitted
- 21.8% to ICU
- 3 deaths (all <4m)
- Only 19 had a history of exposure to someone with a cough!

<table>
<thead>
<tr>
<th>Days of cough before admission</th>
<th>Age</th>
<th>0-4 weeks (n=12)</th>
<th>5-16 weeks (n=51)</th>
<th>≥ 17 weeks (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nil</td>
<td>2 (16.7%)</td>
<td>6 (11.7%)</td>
<td>5 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>≤ 7 days</td>
<td>10 (83.3%)</td>
<td>38 (74.5%)</td>
<td>29 (52.7%)</td>
<td></td>
</tr>
<tr>
<td>8-14 days</td>
<td>0</td>
<td>3 (5.9%)</td>
<td>7 (12.7%)</td>
<td></td>
</tr>
<tr>
<td>≥ 15 days</td>
<td>0</td>
<td><strong>4 (7.8%)</strong></td>
<td><strong>14 (25.5%)</strong></td>
<td></td>
</tr>
</tbody>
</table>

With Thanks to Ute Hallbauer
Cape Town: Retrospective Folder Review

May 2009-December 2012

– 75/305 (25%) PCR-positive, only 14 (19%) notified
– Median age 1.8m
– Cough duration median 7d (IQR 3-14d)
– Sensitivity of WHO definition = 31%

With Thanks to Rudzani Muloiwa
Cape Town: Prospective

September 2012-September 2013

- Inclusion: <13y, <48h after adm, WHO defined pn
- Specimen types – induced sputum & NP swabs
- PCR assays – IS481, IS1001 and hIS1001

With Thanks to Rudzani Muloiwa
Cape Town: Prospective

- Median age 8m (IQR 4-18)
- *Bordetella sp*: 41/460 (8.9%)
- *Bordetella pertussis*: 32/460 (7.0%); NP=17/460 (3.7%)
- No strong signal of seasonality
- Caregiver as source: RR = 13 (8-23)
PERCH (Soweto)

- 2.7% of admissions, 0.5% of controls (OR=6)
- Median cough duration 3d (range 2-15)
- 5 deaths (9.4% of deaths), OR = 4

<table>
<thead>
<tr>
<th></th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-negative Case</td>
<td>HIV-negative Case</td>
<td>HIV-positive Case</td>
<td>Community Control</td>
<td>HIV-infected Control</td>
</tr>
<tr>
<td>(n=803)</td>
<td>(n=116)</td>
<td>(n=829)</td>
<td>(n=829)</td>
<td>(n=135)</td>
</tr>
<tr>
<td>Pertussis Pos</td>
<td>23 (2.9%)</td>
<td>2 (1.7%)</td>
<td>4 (0.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pertussis Neg</td>
<td>780</td>
<td>114</td>
<td>825</td>
<td>135</td>
</tr>
</tbody>
</table>

**Statistical Comparisons**

<table>
<thead>
<tr>
<th></th>
<th>a,b</th>
<th>b,d</th>
<th>c,d</th>
<th>a,c</th>
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<tbody>
<tr>
<td></td>
<td>OR 1.68 (95% CI, 0.41-14.9), P=0.759</td>
<td></td>
<td></td>
<td>OR 6.01 (95% CI, 2.06-24.28), P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>P=0.213</td>
<td></td>
<td>P=1.000</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

With Thanks to David Moore
RMMCH: Prospective

- Enrolled if hospitalised since 15 August 2013 AND:
  - ≤ 10y and Cough ≥ 7d or Cough with any of paroxysms, whoop, apnoea, cyanosis, hypoxia or gagging; OR
  - ≤ 1y with apnoea
Public & Private Sectors (2003-10)

<table>
<thead>
<tr>
<th>Lab</th>
<th>Suspected &amp; tested</th>
<th>PCR +</th>
<th>Culture +</th>
<th>Total confirmed</th>
<th>Detection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHLS</td>
<td>734</td>
<td>82</td>
<td>15</td>
<td>97</td>
<td>13%</td>
</tr>
<tr>
<td>Lancet</td>
<td>1615</td>
<td>165</td>
<td>-</td>
<td>165</td>
<td>10%</td>
</tr>
<tr>
<td>Ampath</td>
<td>985</td>
<td>155</td>
<td>-</td>
<td>155</td>
<td>16%</td>
</tr>
<tr>
<td>Total</td>
<td>3334</td>
<td>402</td>
<td>15</td>
<td>417</td>
<td>13%</td>
</tr>
</tbody>
</table>

With Thanks to Juno Thomas
LABORATORY-CONFIRMED PERTUSSIS IN THE PUBLIC HEALTH SECTOR, 2008-2011

Brett Archer, Warren Lowman, Ranmini Kularatne, Gary Reubenson, Juno Thomas

1 Division of Surveillance, Outbreak Response and Travel Health, National Institute for Communicable Diseases (NICD) of the National Health Laboratory Service (NHLS); 2 NHLS Infection Control Services Laboratory; 3 Department of Clinical Microbiology and Infectious Diseases, School of Pathology, University of the Witwatersrand; 4 NHLS Helen Joseph Hospital; 5 Department of Paediatrics and Child Health, Rahima Moosa Mother and Child Hospital, University of the Witwatersrand

<table>
<thead>
<tr>
<th>Province</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>Total 2008-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cape</td>
<td>2 (3)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Free State</td>
<td>12 (20)</td>
<td>6 (24)</td>
<td>19 (26)</td>
<td>69 (45)</td>
<td>106 (34)</td>
</tr>
<tr>
<td>Gauteng</td>
<td>44 (73)</td>
<td>6 (24)</td>
<td>14 (19)</td>
<td>58 (38)</td>
<td>122 (39)</td>
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<tr>
<td>KwaZulu-Natal</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>2 (1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
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<tr>
<td>North West</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td>4 (3)</td>
<td>7 (2)</td>
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<tr>
<td>Western Cape</td>
<td>0 (0)</td>
<td>13 (52)</td>
<td>39 (53)</td>
<td>17 (11)</td>
<td>69 (22)</td>
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<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>60 (100)</td>
<td>25 (100)</td>
<td>74 (100)</td>
<td>152 (100)</td>
<td>311 (100)</td>
</tr>
</tbody>
</table>

Age Group [% of total]

- <1m
- 1m
- 2m
- 3m
- 4m
- 5m
- 6m
- 7m
- 8m
- 9m
- 10m
- 1y
- 2y
- 3y
- 4y
- 5-9y
- >10y
NHLS CDW-mined data: 2011-July 2014

*B. pertussis* culture & PCR (IS481):

<table>
<thead>
<tr>
<th>Year</th>
<th>EC</th>
<th>FS</th>
<th>GP</th>
<th>KZN</th>
<th>LP</th>
<th>MP</th>
<th>NC</th>
<th>NW</th>
<th>WC</th>
<th>Total</th>
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<tbody>
<tr>
<td>2011</td>
<td>1</td>
<td>86</td>
<td>59</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>23</td>
<td>177</td>
<td></td>
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<tr>
<td>2012</td>
<td>1</td>
<td>18</td>
<td>36</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>23</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td>13</td>
<td>17</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>21</td>
<td>59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014*</td>
<td>3</td>
<td>8</td>
<td>9</td>
<td>6</td>
<td>2</td>
<td>21</td>
<td></td>
<td>49*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>125</td>
<td>121</td>
<td>8</td>
<td>11</td>
<td>10</td>
<td>1</td>
<td>91</td>
<td>372</td>
<td></td>
</tr>
</tbody>
</table>

*Until July 2014*

With Thanks to Juno Thomas
### Monthly Pertussis Surveillance Report: 01 January to 31 July 2014

**Report prepared by:** Outbreak Response Unit, Division of Public Health Surveillance and Response, NICD-NHLS  
**In collaboration with:** National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW), Centre for Respiratory Diseases and Meningitis NICD-NHLS, Lancet, Ampath and Pathcare Laboratories

---

#### Table 1: Number of laboratory-confirmed *B. pertussis* cases by laboratory and month of specimen collection, South Africa, 2013 and 2014

<table>
<thead>
<tr>
<th></th>
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<td>5</td>
<td>2</td>
<td>0</td>
<td>#</td>
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</tr>
<tr>
<td>Feb</td>
<td>3</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>2*</td>
</tr>
<tr>
<td>Mar</td>
<td>1</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>2*</td>
</tr>
<tr>
<td>Apr</td>
<td>3</td>
<td>7</td>
<td>3</td>
<td>4</td>
<td>12</td>
<td>1*</td>
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<tr>
<td>May</td>
<td>8</td>
<td>9</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>#</td>
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<tr>
<td>Jun</td>
<td>4</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>#</td>
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<td>4</td>
<td>5</td>
<td>#</td>
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<tr>
<td>Aug</td>
<td>5</td>
<td></td>
<td>3</td>
<td></td>
<td>#</td>
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</tr>
<tr>
<td>Sep</td>
<td>2</td>
<td></td>
<td>2</td>
<td></td>
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<tr>
<td>Oct</td>
<td>2</td>
<td></td>
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<td></td>
<td>#</td>
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<tr>
<td>Nov</td>
<td>7</td>
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<td>1</td>
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</tr>
<tr>
<td>Dec</td>
<td>5</td>
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<td>2</td>
<td></td>
<td>#</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>59</strong></td>
<td><strong>44</strong></td>
<td><strong>30</strong></td>
<td><strong>17</strong></td>
<td><strong>27</strong></td>
<td><strong>5</strong></td>
</tr>
</tbody>
</table>

# Data not available at the time of generating this report  
* Data incomplete
ENHANCED SURVEILLANCE FOR ADDITIONAL RESPIRATORY PATHOGENS, 2012-2013

Maimuna Carrim1, Halima Dawood5, John Frean2, Melony Fortuin-de Smidt2, Desiree du Plessis2, Mignon du Plessis1, Fahima Moosa1, Jocelyn Moyes1, Fathima Naby5, Nazir Ismail3, Bhavani Poonsamy2, Sibongile Walaza1, Nicole Wolter1, Ebrahim Variava4, Anne von Gottberg1

1Centre for Respiratory Diseases and Meningitis, NICD
2Centre for Opportunistic, Tropical and Hospital Infections, NICD
3Centre for Tuberculosis, NICD
4Department of Medicine, Klerksdorp-Tshepong Hospital
5Pietermaritzburg Metropolitan Hospital and University of KwaZulu-Natal

Bacterial pathogens

Bordetella pertussis

Among the 3664 patients with severe respiratory infection and influenza-like illness who were tested for bacterial pathogens, 42 (1%) were positive for *B. pertussis* of which 31 (74%) presented with SRI and 11 (26%) with ILI. The majority of cases occurred in the winter and spring months (figure 2), and cases occurred at all study sites (figure 3). The highest detection rates of *B. pertussis* were in the 25-44 (17/1230, 1.4%) and 45-64 (10/549, 1.8%) year age groups (figure 4). Cases of *B. pertussis* were detected either in nasopharyngeal specimens (30/42, 71%), or induced sputa (8/42, 19%) or in both specimen types (4/42, 10%).
Reported to WHO

• 2000: 8
• 2001: 24
• 2002: 5
• 2003: 8
• 2009: 4
• 2011: 181
• 2013: 116

• Almost 900 cases detected 2008-2013!
What now?

• Improved assessment of disease burden:
  – Appropriate investigation of suspected cases
  – Ongoing surveillance & case-control studies
  – Vaccine effectiveness
  – Mortality burden
  – Collation of data

• ?Vaccine Evasion

• Change vaccination strategy
  – Maternal vaccination
  – Tdap instead of Td
  – Adolescents
The Pertussis Problem

Stanley A. Plotkin

Table 1. Possible Vaccination Strategies to Control the Resurgence of Pertussis

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Remarks</th>
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<tbody>
<tr>
<td>Return to the use of wcP</td>
<td>Probably unacceptable</td>
</tr>
<tr>
<td>Develop less-reactogenic wcP</td>
<td>Not yet done</td>
</tr>
<tr>
<td>Maternal vaccination to provide transplacental antibody to protect newborn</td>
<td>Now generally recommended</td>
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<tr>
<td>Vaccination of newborn contacts (cocoon strategy)</td>
<td>Difficult to obtain complete coverage</td>
</tr>
<tr>
<td>More frequent boosters with acP</td>
<td>Costly and difficult to put in place</td>
</tr>
<tr>
<td>Change antigens in acP to those from currently circulating strains</td>
<td>Uncertain effect</td>
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<tr>
<td>Increase quantities of current antigens</td>
<td>Would require large trials</td>
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<tr>
<td>Inactivate PT by genetic mutation or milder chemical</td>
<td>Probably advisable to increase immunogenicity</td>
</tr>
<tr>
<td>Add new virulence factors</td>
<td>Would require large trials</td>
</tr>
<tr>
<td>Use stronger adjuvants</td>
<td>May require large trials</td>
</tr>
<tr>
<td>Administer live attenuated <em>Bordetella pertussis</em> intranasally</td>
<td>Early development Probably best as a boost strategy</td>
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